

Applicant : Xiaobin Zhao  
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Attorney's Docket No.: 09736-264001

### REMARKS

The Examiner rejected claims 1, 2, 4, 9, 12-15, 18-21, 24-26, 29, and 36, and objected to claims 5-8 and 11. Claim 36 has been canceled herein without prejudice. Applicant has amended page 4 of the specification to add a Brief Description of the Drawings. The drawings were included with the application as originally filed. The drawings also were described at page 25, lines 12-23 of the specification as originally filed. Thus, no new matter has been added.

In light of these amendments and the following remarks, Applicant respectfully requests reconsideration and allowance of claims 1, 2, 5-8, 11-15, 18-21, 24-26, and 29.

#### Objection to the Specification

The Examiner maintained the objection to the specification as not containing a Brief Description of the Drawings. Applicant has again added a Brief Description of the Drawings to page 4 of the application. Thus, Applicant respectfully requests that the Examiner withdraw the objection to the specification.

#### Rejections under 35 U.S.C. § 102

The Examiner maintained the rejection of claims 1, 2, 4, 12, 13, 15, 18, 20, and 21 under 35 U.S.C. § 102(b) as being anticipated by the Tomihata *et al.* reference (*J. Biomed. Mat. Res.* 1997, 37:243-251). The Examiner also rejected claim 36 under 35 U.S.C. § 102(b) as being anticipated by the Tomihata *et al.* reference, stating that the Tomihata *et al.* reference discloses a cross-linked HA film containing amide and ester bonds. The Examiner further stated that Applicant's declaration filed on December 13, 2004 is insufficient to overcome the rejection of the claims because Applicant failed to set forth sufficient evidence to rebut the *prima facie* case. Applicant's declaration stated that, based on the teachings of U.S. Patent No. 6,096,727 (the '727 patent) and PCT publication no. WO 00/54762, reacting HA with carbodiimide will result in an acylurea bond, not an ester bond as taught by the Tomihata *et al.* reference. The Examiner stated, however, that the reaction conditions of the '727 patent and the Tomihata *et al.* reference are very different, as the Tomihata *et al.* reference teaches cross-linking HA in the presence of a water-soluble carbodiimide (WSC) and L-lysine or L-lysine methyl ester. The Examiner also stated that the Tomihata *et al.* reference discloses that the most prominent difference in the IR

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spectrum between non-cross-linked HA and HA cross-linked with WSC is noticeable at a wavenumber of  $1700\text{ cm}^{-1}$ , which is assigned to the carbonyl group most likely of an ester bond. Thus, the Examiner concluded that the Tomihata *et al.* reference anticipates present claims 1, 2, 4, 12, 13, 15, 18, 20, 21, and 36.

Applicant respectfully disagrees. The present claims recite a process for the preparation of multiple cross-linked derivatives of HA, wherein the cross-linking is effected by contacting HA with one or more chemical cross-linking agents so as to form two or more different types of functional bonds between the HA molecules, and wherein the two or more different types of functional bonds are selected from the group consisting of ether, ester, sulfone, amine, imino, and amide bonds. Referring again to the declaration by Xiaobin Zhao and the corroborating evidence (U.S. Patent No. 6,096,727 and PCT Publication No. WO 00/54762) submitted on December 13, 2004, the teachings of the Tomihata *et al.* reference are incorrect, as the procedures disclosed therein do not result in HA molecules cross-linked to one another by two or more types of bonds as set forth in present claim 1. The Tomihata *et al.* reference reports that reacting HA with WSC resulted in an ester bond. This conclusion seems to be based on speculation, as Tomihata *et al.* assigned the peak at  $1700\text{ cm}^{-1}$  in the IR spectra of cross-linked HA to the carbonyl group most likely of an ester bond. In contrast, the '727 patent discloses that reacting HA with WSC results in an acylurea bond. *See*, the '727 patent at, *e.g.*, column 3, lines 30-36. Further, Applicant notes that acylurea bonds also contain a carbonyl group (*see*, column 7, lines 1-24 of the '727 patent), which could result in the increased peak at  $1700\text{ cm}^{-1}$  that was observed by Tomihata *et al.*

As noted by the Examiner, the '727 patent does not disclose cross-linking HA in the presence of both WSC and a primary amine such as L-lysine methyl ester. Applicant notes, however, that when responding to Applicant's arguments, the Examiner must address all arguments that have not already been responded to in the statement of the rejection. *See*, the Examiner Note under Form Paragraph 7.37, MPEP § 707.07(f). In the present case, the Examiner appears to have ignored the teachings of PCT Publication No. WO 00/54762, which also was submitted in response to the previous Office Action. The WO 00/54762 publication discloses that reacting a carbodiimide with HA results initially in O-acylisourea linkages that, in the presence of a nucleophile such as a primary amine, are converted to amide linkages as well as

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N-acylurea linkages. Consistent with the '727 patent, the PCT publication further discloses that in the absence of a nucleophile, rearrangement from the O-acylisourea to the N-acylurea is the predominant reaction. *See*, WO 00/54762 at page 6, line 30 to page 7, line 6. Thus, the teachings of the '727 patent and WO 00/54762 both contradict the teachings of the Tomihata *et al.* reference.

Moreover, the Bulpitt and Aeschlimann reference (*J. Biomed. Mater. Res.* (1999) 47:152-169; copy submitted herewith) provides further support for the inaccuracy of the Tomihata *et al.* reference. Consistent with the '727 patent and WO 00/54762, the Bulpitt and Aeschlimann reference discloses that reaction of HA with a carbodiimide results in a stable acylurea bond. *See, e.g.*, the second full paragraph on page 153 and Figure 2 on page 154 of the Bulpitt and Aeschlimann reference. The second full paragraph on page 153 of this reference also discloses that reaction of HA with both a carbodiimide and a primary amine results primarily in formation of a stable N-acylurea bond, and "any amide formation that does occur is insignificant." Taken together, the '727 patent, WO 00/54762, and the Bulpitt and Aeschlimann reference disclose that reacting HA with WSC will not yield an ester bond, regardless of whether a primary amine such as L-lysine methyl ester is present, and formation of an amide bond is questionable even in the presence of a primary amine such as L-lysine methyl ester. Thus, these references in combination teach that the disclosure of the Tomihata *et al.* reference is incorrect, and suggest that at best, Tomihata *et al.* prepared HA cross-linked by acylurea and perhaps amide bonds. As such, Applicant has provided sufficient evidence to rebut the Examiner's rejection, and the Tomihata *et al.* reference does not anticipate the present claims.

In light of the above, Applicant respectfully requests withdrawal of the rejection of claims 1, 2, 4, 12, 13, 15, 18, 20, and 21 under 35 U.S.C. § 102(b).

#### Rejection under 35 U.S.C. § 103

The Examiner maintained the rejection of claims 1, 2, 4, 9, 12-15, 18-21, 24-26, and 29 under 35 U.S.C. § 103(a) as being unpatentable over the Tomihata *et al.* reference in combination with U.S. Patent No. 5,690,961 (the '961 patent). As above, the Examiner stated that the declaration by Xiaobin Zhao filed December 13, 2004 is insufficient to rebut the *prima facie* case.

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Applicant respectfully disagrees. Again, the teachings of the Tomihata *et al.* reference are not accurate. Given the teachings of the '727 patent, WO 00/54762, and the Bulpitt and Aeschlimann reference discussed above, a person having ordinary skill in the art at the time Applicant filed would have been well aware of the inaccuracies of the Tomihata *et al.* reference, and would have appreciated that reacting HA with a carbodiimide would result in acylurea bonds rather than ester bonds. In fact, a person having ordinary skill in the art would have appreciated that the Tomihata *et al.* reference suggests, at most, using carbodiimide to crosslink HA and at no point discloses any teaching that provides a skilled artisan with a reasonable expectation of success in achieving HA crosslinked with an ester bond.

The Nguyen patent discloses HA cross-linked with polyanhydrides, as well as HA cross-linked to polycarboxylic acids. *See, e.g.*, column 3, lines 13-33 of the Nguyen patent. At no point, however, does the Nguyen patent suggest that a person of ordinary skill in the art should make HA cross-linked through two or more different types of bonds selected from the group consisting of ether, ester, sulfone, amine, imino, and amide bonds as recited in present claim 1. Taken together, a skilled artisan following the teachings of the Tomihata *et al.* reference and the Nguyen patent would not have arrived at HA cross-linked with two or more types of bonds as recited in claim 1. This is especially true given that HA cross-linked with carbodiimide was known to result in an acylurea bond, not an ether, ester, sulfone, amine, imino, or amide bond. Thus, the combination of cited references fails to render the present claims obvious.

In light of the above, Applicant respectfully requests withdrawal of the rejection of claims 1, 2, 4, 9, 12-15, 18-21, 24-26, and 29 under 35 U.S.C. § 103(a).

#### Claim Objections

The Examiner objected to claims 5-8 and 11 as being dependent upon a rejected base claim. The Examiner stated that these claims would be allowable if rewritten in independent form the include all of the limitations of the base claim and any intervening claims. Applicant acknowledges the Examiner's statement regarding claims 5-8 and 11. In view of the remarks presented herein, Applicant has not amended these claims.

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### CONCLUSION

Applicant submits that claims 1, 2, 4-8, 11-15, 18-21, 24-26, and 29 are in condition for allowance, which action is respectfully requested. The Examiner is invited to telephone the undersigned agent if such would further prosecution.

Applicant believes no fee is due for filing this Amendment and Reply. Please apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

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